

EDITORIAL COMMENT

# Patients With Atrial Fibrillation and a CHA<sub>2</sub>DS<sub>2</sub>-VASc Score of 1

## Are They at Low or High Stroke Risk?\*

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Nonvalvular atrial fibrillation carries a risk for developing ischemic stroke that is lowered by anticoagulant therapy (1). This risk is not uniform and depends on whether a patient has either none or  $\geq 1$  of the following factors, known as the CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk score: congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category. Both European (2) and U.S. (3) guidelines advocate estimation of a patient's stroke risk by use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score for initial risk stratification. The European Society of Cardiology (ESC) guideline recommends oral anticoagulant therapy (OAC) for male patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 1$  and for female patients with a score  $\geq 2$  (the latter because this guideline does not classify female sex as a stand-alone risk factor). The U.S. guideline recommends use of OAC at a CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk score  $\geq 2$  for patients of both sexes.

Decision making for thromboprophylaxis by antithrombotic therapy must balance the risk of stroke against the risk of major bleeding, especially intracranial hemorrhage, which is the most feared complication because it confers a high risk of death and disability. For optimal balancing of stroke and bleeding risk, net clinical benefit has been defined as

the annual rate of ischemic strokes and systemic emboli prevented by OAC minus the rate of intracranial hemorrhages attributable to OAC, multiplied by an impact weight (4,5). A recent Markov decision analysis model suggested that vitamin K antagonists are preferable in patients with a stroke risk  $\geq 1.7\%$  per year, whereas treatment with the safer non-vitamin K oral anticoagulants should be considered in patients with a stroke risk  $\geq 0.9\%$  per year (6).

Where do we stand in applying the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in clinical practice and how robust are the data on which the application of CHA<sub>2</sub>DS<sub>2</sub>-VASc score in the guidelines is currently based? There is little or no doubt of the need for OAC in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of  $\geq 2$  and of the very low-risk status in those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0. However, because there are large differences in estimates of stroke risk without antithrombotic treatment, the real focus of debate is in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1. Thus, studies have shown a 3-fold difference in the annual stroke risk in AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 and no OAC treatment, varying from 0.6% to  $>2.0\%$  (7).

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In this issue of the *Journal*, Lip et al. (8) assessed the stroke event rate in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 to 1 in a Danish hospital cohort. They observed a 1-year rate of stroke of 0.49% (intention-to-treat) in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 and a score of 1.55% (intention-to-treat) in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1. These rates are comparable to an earlier analysis from Denmark, in which a rate of 2.01% was seen (9), but much higher than in the original publication validating the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (10). In that publication, in the 103 patients who participated in the Euro Heart Survey 2006

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registry with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score of 0 and not treated with either OAC or aspirin, the annual thromboembolic rate (defined by ischemic stroke and other thromboembolic events) was 0%. For the 162 patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score of 1, this annual risk was 0.6%. Of note, in the 2010 version of the ESC atrial fibrillation guidelines, a patient with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score of 1 has a much higher stroke risk of 1.3% (11). This is not a rate derived from an untreated population but a post-hoc calculated stroke risk from analysis of warfarin-treated patients from the 2 SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) ximelagatran studies adapted for a presumed lack of effect of warfarin treatment (12). One wonders why the 2010 ESC guidelines incorporated this risk and not the original untreated annual stroke risk of 0.6% from the validation study.

The rate observed in the current study by Lip et al. (8) is also much higher than in a large Swedish cohort recently published in the *Journal* (7). In that study, the annual stroke rate was 0.1% to 0.2% for women with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score of 1; for men, the ischemic stroke rate was 0.5% according to the Swedish Riks-Stroke and 0.7% according to the Swedish National Patient Register. A closer look at the study of Friberg et al. teaches us important lessons. First, if a wide definition of stroke was used (i.e., if it included hospital discharge diagnoses of stroke, transient ischemic attack, pulmonary embolism, arterial embolism, and stroke not specified as ischemic or hemorrhagic), the annual event rate for men increased by 44% to 1.3%. Second, Friberg et al. investigated the influence of the so-called quarantine period, used to avoid counting strokes that are concomitant with the first index diagnosis of AF, which can lead to spuriously elevated stroke rates. After 4 weeks, event rates stabilized at a level almost one-half as high, as if no quarantine period had been used. How did Lip et al. account for these variations? According to their Online Table w3, the 1-year stroke rates were reduced from 1.46% (continuous treatment) to 1.18% when using only primary discharge diagnoses of ischemic stroke, and it was lowered further to 0.96% with full follow-up. This latter figure is very near the cutoff for starting non-vitamin K oral anticoagulants (6). Because the quarantine period was only 14 days, it is unknown whether the rates would have been even lower, had a longer, more reasonable quarantine period of 4 weeks been used.

The most important drawback of the current studies is that all CHA<sub>2</sub>DS<sub>2</sub>-VASC validation exercises have been performed by retrospective collection of data in so-called “real-world” registries. It is therefore uncertain on what grounds physicians have selected their patients for treatment with OAC, aspirin, or no treatment. All calculations of CHA<sub>2</sub>DS<sub>2</sub>-VASC scores in these studies have clearly been performed post-hoc. Ideally, randomized trials should clarify this issue. Importantly, ongoing, large international prospective registries, including GARFIELD (Global Anticoagulant Registry in the FIELD) (13) and GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation) (14), which are studying the consequences of CHA<sub>2</sub>DS<sub>2</sub>-VASC risk score estimation with respect to starting “yes or no” with antithrombotic treatment, may yield a more accurate estimate of the stroke risk compared with the retrospective, single-country (e.g., Swedish and Danish) databases that seem to point in opposite directions (7,8).

Thus, although the CHA<sub>2</sub>DS<sub>2</sub>-VASC score has rightly been introduced into the clinical arena as a useful adjunct to the CHADS<sub>2</sub> score (i.e., congestive heart failure, hypertension [i.e., blood pressure consistently above 140/90 mm Hg, or treated hypertension on medication], age  $\geq 75$  years, diabetes mellitus [1 point for presence of each], and stroke/transient ischemic attack [2 points]), the current literature demonstrates that the CHA<sub>2</sub>DS<sub>2</sub>-VASC score has obviously been retrospectively validated in different patient populations, leading to markedly different estimated stroke risks. We are therefore left with uncertainty as to the true stroke rate in untreated patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score of 1. This uncertainty should be incorporated into guidelines, thus enabling clinicians to build it into the decision process when confronted with their next patient presenting with nonvalvular atrial fibrillation. On the basis of current evidence, there is still equipoise as to whether a patient with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score of 1 carries a low or a high stroke risk.

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